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Hepatoma of the liver – resection or transplantation?

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Abstract *Introduction:* Despite recent advances with techniques of in situ tumor ablation, surgical therapy remains at present the mainstay in the treatment of primary hepatic malignancies. *Discussion:* After an initial endeavor to establish liver transplantation as a treatment option, especially for unresectable liver tumors, only a few indications, for example early hepatocellular carcinoma in cirrhosis, are currently agreed upon. Other indications, such as peripheral cholangiocarcinoma and hepatocellular carcinoma in non-cirrhotics, have largely been abandoned or are still under debate, as with fibrolamellar carcinoma. Selection of patients suffering from hepatocellular carcinoma in cirrhosis for liver transplantation is still based on tumor size and node number, because the current state of diagnostic imaging fails to reliably predict the most important prognostic parameter: vascular infiltration. Other selection criteria are under investigation. Studies on multimodal therapy are also underway but have not yet demonstrated a benefit.

Key words Hepatoma · Liver resection · Liver transplantation

Introduction

The terms hepatoma or primary liver cancer are frequently used synonymously with primary hepatocellular carcinoma. However, there is a huge variety of malignant epithelial and mesenchymal liver tumors to which the term „hepatoma" may be applied (Table 1). Hepatocellular carcinoma is by far the most prevalent tumor, followed by cholangiocarcinoma. In a worldwide perspective, hepatocellular carcinoma and cholangiocarcinoma account for 84% and 13% of all primary liver tumors, respectively [1]. So far, surgical resection has remained the mainstay for treatment of primary liver tumors, as it may provide consistent long-term tumor-free survival. The more profound understanding of the anatomic and physiologic basis of liver surgery, especially of segmental anatomy and hepatic regeneration, as well as a marked progress of anesthesiology and surgical technique have resulted in a substantial increase in the total number and safety of hepatic resection. Various resective procedures with different degrees of segment – or lobectomies have represented the standard in the treatment of malignant neoplasia of the liver. Postoperative mortality and fatalities due to recurrence of the tumor or complications of cirrhosis have impaired outcome, especially in the treatment of hepatocellular carcinoma in cirrhosis. Other therapeutic practices, such as total hepatectomy and liver transplantation, percutaneous ethanol in-

Table 1 Epithelial and mesenchymal primary liver tumors

Epithelial liver tumors	Mesenchymal liver tumors
Hepatocellular carcinoma	Angiosarcoma
Cholangiocarcinoma	Rhabdomyosarcoma
Hilar (central) bile duct cancer	Neuroblastoma
	Malignant histiosarcoma
	Leiomyosarcoma
	Lymphoma
	Endodermal sinusoidal tumor
	Undifferentiated sarcoma

jection, transarterial chemoembolization, laser-induced thermotherapy, radio frequency thermoablation, and photodynamic therapy have, at least in part, also resulted in favorable survival figures and could emphasize the need for revision of standardized therapeutic strategies [2, 3, 4, 5, 6].

Almost all of these investigational efforts aim at an improvement of the therapy of hepatocellular carcinoma, whereas cholangiocarcinoma can only rarely be found in the focus of interest. This neglect is only in part due to its relative rarity when compared with hepatocellular carcinoma. It appears even more important that cholangiocarcinoma must be linked to chronic liver diseases to a much lesser extent than hepatocellular carcinoma and can, therefore, only by chance be detected as a small sub-clinical and resectable mass.

Other primary hepatic neoplasms are only exceptionally encountered in the surgical practice. Reports on the experience with surgical therapy are limited to small series or even case reports and do not allow for conclusions on specific therapeutic guidelines, which in consequence roughly follow those for other liver tumors.

Hepatocellular carcinoma

In the treatment of primary hepatocellular carcinoma confined to the liver, surgical resection is the most likely treatment to result in long-term survival. Nevertheless, two factors qualify such a therapeutic concept. First, the proportion of patients eligible for surgical resections still varies from 8% to 40%, though it has constantly increased in the course of intensified screening efforts [7, 8, 9, 10, 11]. Second, this subset of patients is likely to suffer from tumors responding to other treatment options as well, for example, percutaneous ethanol injection or laser-induced thermotherapy. Convincing data which could conclusively determine that surgical resection compares favorably with in situ ablation of the tumor or vice versa are not at hand. Studies are underway, and surgical resection will prevail as the therapeutic standard as long as the uncertainty remains with regard to its alternatives.

One important caveat has to be considered concerning those patients suffering from hepatocellular carcinoma in liver cirrhosis. Only half of the patients dying in the course of the disease do so due to the liver tumor or its metastases, which occur less frequently than in many other malignant conditions. The remaining fatalities are to be ascribed to the underlying chronic liver disease [12]. Today, liver transplantation is the only simultaneous treatment of primary liver disease as well as of hepatocellular carcinoma. As about 80% of all hepatocellular carcinomas develop within cirrhotic liver tissue, which is considered as a risk factor for malignant transformation, most patients have to be evaluated regarding the therapeutic potential of liver transplantation with respect to their primary disease. The problem of de novo hepatocellular carcinoma within cirrhotic livers or of overlooked small satellites has been addressed by Belghiti et al. [13]. Analyzing 47 patients after liver resection of hepatocellular carcinoma and cirrhosis with a cleared resection margin of at least 1 cm, a rate of intrahepatic recurrence of 60% (n=28) was reported. Most (86%) recurrent intrahepatic tumors were detected in a distance to the resection margin of at least 2 cm. Overall 5-year survival after liver resection was 17%. To determine treatment options, it is necessary to distinguish between patients suffering from hepatocellular carcinoma in cirrhosis and those without liver cirrhosis.

Hepatocellular carcinoma in cirrhosis

No phase-III trials comparing resection with total hepatectomy and liver transplantation have been done. In view of the scarcity of the resources and, even more important, the unmatched long-term survival rates in selected patients suffering from hepatocellular carcinoma in cirrhosis undergoing total hepatectomy and liver transplantation, it appears unlikely that such a trial will ever be performed. A crucial factor still requiring further investigation is the appropriate selection of patients. TNM and *Union Internationale Contre le Cancer* (UICC) classification of hepatocellular carcinoma must be considered with caution for therapeutic decision making because they comprise biologically different tumors in common categories – for example, carcinomas with and without vascular invasion in T stages 1 to 3 or formerly lymph-node positive and negative tumors in UICC stage III, which has therefore recently been split into stages UICC IIIa and IIIb.

Selection has to rule out those patients in whom the cancer has extended beyond hepatic confines from becoming candidates for liver transplantation. Gross metastases or lymph-node infiltration as indicators of an extrahepatic spread may easily be detectable pretransplant by imaging procedures or laparoscopic staging [14, 15]. However, the current state of pretransplant and even intraoperative diagnostic imaging fails as yet to reliably distinguish between patients suffering from hepatocellular carcinoma in cirrhosis with or without a vascular infiltration. In liver transplantation, the problem of a microscopic tumor cell dissemination is of paramount importance because post-transplant immunosuppression appears to alter tumor cell kinetics. The increased risk of intrahepatic recurrence and limited survival under immunosuppression has been shown in a study by Yokoyama et al., who found a much shorter tumor volume doubling time (TVDT) of recurrent hepatocellular carcinomas after transplantation than after resection (33±7 days vs 274±79 days) [16]. This finding was supported in a detailed study

by Panis et al., who injected colo-rectal tumor cells into the portal vein of rats [17]. Eight weeks after tumor cell injection, only the rats without liver tumors were selected for randomization into three groups. One served as a control group, another received cyclosporin, and in one a standardized liver resection was performed. The noteworthy results showed a significantly higher rate of liver tumors in the cyclosporin-treated group (80%) when compared with the control group (29%).

Bismuth et al. were the first to show that in the early era of liver transplantation, the surgical strategy for the treatment of hepatocellular carcinoma in cirrhosis had followed a misconception in selecting patients suffering from advanced and, therefore, unresectable cancers, as transplant candidates [18]. Even groups advocating liver transplantation to continue through as a therapeutic option for selected patients suffering from unresectable liver tumors of various anatomical origins recommended excluding UICC stages III and IV hepatocellular carcinoma from liver transplantation alone [19]. Based on United Network of Organ Sharing (UNOS) and European Liver Transplant Registry (ELTR) data, patient survival was poor and reached only 30% 5 years post-transplant. Conversely, small hepatocellular carcinomas (in cirrhosis) with diameters of less than 3 cm, comprising only one or two nodules, that means tumors frequently suitable for resection, showed favorable outcome. The results of Bismuth's group have been confirmed in another study of six French centers showing a 60% rate of 5-year disease-free survival in patients undergoing liver transplantation [20]. This figure is significantly higher than the 14% 5-year disease-free survival rate in patients undergoing liver resection. Independent prognostic factors were again tumor size and number of tumor nodules. In addition, vascular invasion could be identified as a prognostic factor in the study by Selby et al., in which hepatocellular carcinomas of UICC stages I to III carried an acceptable 5-year survival of about 60%, whereas UICC IVa reflecting vascular invasion and disseminated tumor nodules showed a significantly poorer prognosis (5-year survival 11%) [21]. The results of the aforementioned studies do not originate from randomized trials. Therefore, the groups undergoing resection or transplantation are certainly not comparable.

The most favorable results originate from groups applying selection criteria that do not adhere stringently to the TNM classification but to size and number of tumor nodules. Patients suffering from hepatocellular carcinoma and cirrhosis with three or less tumor nodules, a maximum diameter not exceeding 5 cm, and no signs of vascular invasion underwent the evaluation process which would also be required for transplant candidates with other, mostly benign indications for liver transplantation. Table 2 shows the recently obtained survival data of the groups from Milan and Barcelona as well as our own results [22, 23]. These independently performed studies generated a consistent 75% figure of 5-year survival (Milan: 4-year survival) post-transplant and are likely to support the criteria as surrogate markers for the absence of a vascular infiltration which would otherwise be impossible to be ruled out.

In our experience three factors account for this favorable long-term prognosis:

1. No operative fatalities occurred, whereas the postoperative mortality ranges from 3% to 15% after liver resections performed in patients suffering from cirrhosis.
2. Rates of tumor recurrence were low as a total hepatectomy should always be considered as formally curative. In particular, atypical or wedge resections performed due to a limited functional hepatic reserve frequently do not succeed in achieving sufficiently cleared resection margins and bear the risk of overlooked satellite nodules. Moreover, a total hepatectomy offers the possibility of complete histopathologic staging for detection of multicentricity or small satellite nodules. In contrast, staging based on diagnostic imaging will probably generate false-negative results by missing smaller satellites in the future remnant liver. Interestingly, the aforementioned study of Bismuth et al. had also disclosed that 3-year survival of patients suffering from small hepatocellular carcinoma in cirrhosis (<3 cm) was only 39% and was worse than a 3-year survival figure of 55% in those with larger nodules (>5 cm) [18]. The authors explained this puzzling paradox with an increased likelihood of undetected nodules in remnant liver tissue when only

Table 2 Results from European liver transplant programs applying comparable selection criteria prior to liver transplantation for hepatocellular carcinoma (HCC) in cirrhosis

Center	Reference	Selection criteria for HCC in cirrhosis	*n*	5-Year survival (%)
Milan	22	Solitary tumors <5 cm; 1–3 nodules, largest nodule <3 cm	48	75[a]
Barcelona	23	Solitary tumors <5 cm; no known vascular infiltration	58	74
Berlin		Solitary tumors <5 cm; 1–3 nodules, largest nodule <3 cm; no known vascular infiltration	73	74

[a] 4-Year survival

one or two small nodules were discovered by repeated screening. In the experience from cases of transplantation, the rate of pretransplant undetected carcinomatous foci in the cirrhotic liver was 24%. This figure was later confirmed by Mazzaferro et al. as well as by our own results [12, 22].

3. The fatal potential of the underlying liver disease, which may be deleterious after resection can almost be ignored after transplantation except for a few patients suffering from recurrent hepatitis B.

In our series of 73 patients undergoing liver transplantation for hepatocellular carcinoma in cirrhosis after fulfilling the selection criteria indicated above, prognostic parameters as number of nodules or maximum diameter of the largest mass did not prove to impact on survival anymore. Upon comparison of patients suffering from UICC stage IVa carcinomas with those suffering from tumors of UICC stages I to III, superior survival could be observed in the group with less advanced tumors. The respective 5-year survival figures were 83% versus 48%. Long-term survival among patients suffering from hepatocellular carcinomas in cirrhosis (UICC stages I to III) was comparable with the 5-year survival rate of patients who had undergone liver transplantation for benign indications (5-year survival 86%). These survival figures of the subgroups corresponded almost identically to those reported by Mazzaferro et al. for patients who eventually did (n=35; 4-year survival 85%) or did not (n=13; 4-year survival 50%) meet pretransplant selection criteria [22].

The UICC stage IVa of hepatocellular carcinoma in this subset of patients is comprised of bilobular tumors and/or tumors involving a major branch of the portal vein or the hepatic veins. It is still a matter of investigation whether only a major vascular infiltration should determine exclusion from a transplant program or also tumor growth in more than one lobe. It is noteworthy that an autopsy study from 1990 showed a frequency of extrahepatic disease increasing with tumor size, histologic type, and number of nodules [24]. The incidence of hematogenous metastases ranged from 14% for single nodules to 82% for a diffuse multinodular tumor disease.

Other markers more directly correlated to vascular infiltration are needed to identify both patients who even though adhering to the currently applied selection criteria do not benefit over the long term and those who are currently excluded due to an inaccurate strictness. It is as yet unknown whether histopathological grading which has so far not been reported in the literature on liver transplantation for hepatocellular carcinoma in cirrhosis or other parameters as DNA-ploidy and factors of angiogenesis will prove to be more reliable than gross pathological markers to determine the true extent of the malignant disease [25, 26, 27, 28]. Another possible strategy to assess the suitability of a patient may be pretransplant transarterial chemoembolization (TACE). This may be a concept which has rather accidentally been generated from a study on multimodal therapy. The group around Bismuth conducted a retrospective analysis of their experience with TACE and failed to show a survival benefit [29]. Interestingly, they could demonstrate significant survival then by separating patients treated with TACE into a group that had responded with tumor necrosis to another group not developing necrosis. Therefore, it should be determined whether chemoembolization might serve as a selection criteria prior to liver transplantation.

It is still a matter of debate whether multimodal therapy will be able to improve outcome [30]. So far, treatment options in conjunction with liver transplantation have been confined to pilot trials involving TACE and postoperative chemotherapy. Olthoff et al. suggested doxorubicin pre-, intra-, and postoperatively with a significant increase of survival when compared with historic controls. However, tumor stages were not well defined and 3-year survival rates did not compare favorably with those published in many series without adjuvant therapy. Prospective randomized trials have not been published so far although they are in progress at different centers.

Hepatocellular carcinoma in non-cirrhotic livers

In general, hepatocellular carcinoma in non-cirrhotic livers occurs considerably less frequently than in cirrhosis, and these fewer tumors are much more advanced. In an autopsy study from Japan involving 618 patients, Okuda et al. reported a rate of only 11% of hepatocellular carcinoma growing in non-cirrhotic livers [31]. There are few data available about hepatocellular carcinomas in non-cirrhotic livers, because this type of tumor is rarely separately identified in series reported in the literature. One of the characteristics of this tumor is its advanced size at diagnosis. Hepatocellular carcinoma in non-cirrhotic livers is mostly not detected before it becomes a palpable mass or symptomatic by pain, fever due to necrosis or rarely by rupture.

In the largest single-center experiences on the treatment of hepatocellular carcinoma in non-cirrhotic livers, Bismuth et al. from Paris and Iwatsuki et al. from Pittsburgh reported 5-year survival rates after liver resection of 40% and 44%, respectively [32, 33]. We have reported a rate of 38% in patients suffering from tumors in UICC stage III, which represent by far the largest group of patients still eligible for treatment in a curative intention [12]. However, some UICC IVa tumors may also undergo surgical therapy because the functional capacity of the liver tissue frequently allows extended liver resections. In the report of Bismuth et al. as well as in our experience, more than 50% of all resections performed for hepatocellular carcinoma in non-cirrhotic livers are hemihepatectomies, and more than 20% are more extended liver resections. These high rates contrast the pre-

dominance of segmental and wedge resections performed for hepatocellular carcinoma in cirrhosis. Nevertheless, even extended liver resections in patients not suffering from liver cirrhosis are associated with a lower postoperative mortality rate. In the two reports of Bismuth et al., the postoperative mortality rate was 3% in non-cirrhotics compared with 10% in cirrhotics. Moreover, late complications after resection of hepatocellular carcinoma and cirrhosis due to the underlying liver disease are responsible for half of the patient deaths over the long term. In patients suffering from hepatocellular carcinoma without liver cirrhosis, tumor recurrence occurs in more than half of the patients and is the main cause of death.

Attempts to improve the treatment of hepatocellular carcinoma in non-cirrhotics by performing total hepatectomy and liver transplantation have failed. These advanced tumors bear a considerable likelihood of a microscopic dissemination and, in consequence, an overwhelming risk of recurrence further increased by immunosuppression. The consistent rates of post-transplant 5-year survival were 26%, reported by Pichlmayr et al. and Iwatsuki et al. [19, 33]. However, both authors identified a subgroup of patients in whom the recommendation not to perform liver transplantation would need to be further substantiated or even withdrawn. These were patients suffering from fibrolamellar carcinoma, an uncommon variant of hepatocellular carcinoma only exceptionally associated with cirrhosis and distinguished by histopathological features suggesting greater differentiation than other hepatocellular carcinoma [35, 36, 37].

As most patients suffering from fibrolamellar carcinoma are young non-cirrhotics, it is uncertain whether a better prognosis after liver resection when compared with patients suffering from conventional hepatocellular carcinoma has in fact to be ascribed to properties of the tumor. So far, data of the less than 200 patients after surgical therapy reported in the literature did not reveal conclusive results. In a registry report on the impact of tumor characteristics of hepatocellular carcinoma on outcome, histological grade, vascular invasion, lymph-node infiltration, and size of the tumor were identified as significant determinants of patients' survival but not the fibrolamellar variant [38]. Ringe et al. have described 20 patients with a mean age of 23 years [39]. Actuarial survival 4 years after transplantation (n=6) was 33%. In the resection group (n=14), 5-year survival was 38%. It was concluded that the fibrolamellar variant could not be confirmed to be an independent indicator of better patient survival.

The largest single-center report originates from Pittsburgh [40]. Pinna et al. described the treatment of fibrolamellar carcinoma with resection (n=28) or transplantation (n=13) in 41 patients. The mean age of the patients was 30 years. Almost all fibrolamellar carcinomas could be assigned to the UICC stages IVa or even IVb with surprising postoperative 5-year survival rates of 66% and 50%, respectively. Comparing patients undergoing liver resection with those in whom liver transplantation had been performed, the 5-year survival rates were 82% and 38%, respectively. Liver resection was consistently superior to liver transplantation over the years, and the gap of 44% at 5 years prevailed also after 10 years. In our opinion, these outstanding results after resection of advanced stage fibrolamellar carcinoma may in fact indicate a prognosis different from that of non-fibrolamellar hepatocellular carcinomas without underlying liver disease. Extended and multivisceral resections which have been performed in many patients reported by Pinna et al. are warranted. However, the problem of recurrent disease after liver transplantation, if the tumor was advanced, cannot be overcome by fibrolamellar carcinoma either. Therefore, liver transplantation is not an appropriate treatment for fibrolamellar carcinoma if the patient is non-cirrhotic. Fibrolamellar carcinoma in cirrhosis follows the concept outlined for hepatocellular carcinoma in cirrhosis.

The question of whether a small, resectable hepatocellular carcinoma without an associated liver cirrhosis would benefit from a total hepatectomy and liver transplantation is rather theoretical because these tumors rarely occur. However, some arguments can be advanced in favor of liver resection or against liver transplantation. First, graft shortage and high costs represent more general problems, demonstrating the narrow limits that have to be considered especially if patients are not suffering from liver cirrhosis as indication for liver transplantation. Second, outcome after resection of hepatocellular carcinoma in non-cirrhotics is not impaired by a high postoperative mortality or long-term failures due to underlying liver diseases. Third, it is still unknown whether hepatocellular carcinomas in cirrhosis and in non-cirrhotics are identical or diverse malignant diseases. There are hints in support of the latter theory. We have, for example, looked for a microscopic tumor cell dissemination into the bone marrow which had been investigated for many gastrointestinal malignancies but not for hepatocellular carcinoma [41]. Our preliminary findings which had been obtained from a group of patients undergoing liver resection for hepatocellular carcinoma disclosed that patients suffering from associated liver cirrhosis appear to have a lower frequency of bone-marrow metastases than patients without liver cirrhosis. This finding merits further investigation but may advocate against liver transplantation for hepatocellular carcinoma in non-cirrhotics.

Cholangiocarcinoma

Cholangiocarcinoma is an adenocarcinoma arising from the intrahepatic biliary epithelium and developing in a

non-cirrhotic liver. It is commonly separated into peripheral and hilar types. According to a widely accepted definition of cholangiocarcinoma, only adenocarcinomas of the peripheral type should be classified as cholangiocarcinoma [42]. The development of cholangiocarcinoma has in some cases been related to the use of thorotrast, hepatolithiasis, hepatic infestation (clonorchis sinensis, opisthorchis viverrine), cystic and dysplatic hepatic lesions (congenital cysts, Caroli's disease), primary sclerosing cholangitis (PSC), and chronic inflammatory bowel disease. The development of cholangiocarcinoma is generally not related to cirrhosis or hepatitis B infection, while an involvement of the hepatitis C virus has at least been suggested [43]. Peripheral cholangiocarcinoma becomes symptomatic by size as they enlarge and patients present with pain, malaise, and fever, whereas the hilar or extrahepatic type is characterized by obstructive jaundice. In areas of frequent association with hepatolithiasis, e.g., Taiwan, as many as 25% of the patients suffering from cholangiocarcinoma undergo surgery for chronic cholangitis [44]. The study from Taiwan gives no details on the tumor stages and it cannot be assessed whether a high rate of concomitant liver disease also resulted in an increased share of less advanced tumors. Pichlmayr et al. gave the most detailed report on the surgical treatment of cholangiocellular carcinoma so far and reported on 50 patients [45]. The rates of patients suffering from UICC stages II, III, or IVa tumors were 26%, 22%, and 48%, respectively. However, data of an association between cholangiocarcinoma and primary liver diseases are not given in this study. This distribution of tumor stages appears comparable with those expected for hepatocellular carcinoma in non-cirrhotics, except for a relatively high share of UICC stage-II tumors. In this study, 32 patients underwent liver resections, more than half of which were extended liver resections. This rate may in part be reflected by 30-day and 60-day mortality rates of 6% and 16%, respectively. Survival at 5 years could only be observed in four patients suffering from T2 tumors. The overall 5-year survival rate was 18%. Interestingly, survival was largely dependent on tumor characteristics reflected by the T-stage, whereas 5-year survival after resection of lymph-node positive and negative tumors was almost identical.

Cherqui et al. have emphasized that an aggressive surgical management is the mainstay in therapy of cholangiocarcinoma if a sufficiently cleared resection margin (more than 1 cm) can be achieved. This report gave only 2-year survival rates, which were 32% for all patients. However, the subset of those with solitary, lymph-node negative tumors and cleared resection margins survived without fatalities.

Unresectable tumors and functional restrictions but also the assumption that great exstirpative procedures might provide an increased chance for cure resulted in the more radical concept of resecting the entire intrahepatic biliary tree by combining hilar resection, total hepatectomy, and liver transplantation. Arguments in favor of this approach included a putative rise in rates of formally curative resections, the simultaneous therapy of underlying or associated diseases, for example primary sclerosing cholangitis, as well as the prevention of de novo and recurrent tumors, since multifocal lesions within the biliary tract may be identified in as many as 10% of patients. Postoperative mortality was even expected to decrease as liver transplants in a patient population not suffering from complicating portal hypertension can be performed rather straightforwardly. However, postoperative and long-term survival figures have been disappointing.

In a review of 34 patients originating from 13 studies, 90-day mortality and 5-year survival rates after total hepatectomy and liver transplantation for peripheral cholangiocarcinoma were approximately 29% and 6%, respectively [46]. Cancer recurrence predominated as cause of death in 88% of the patients surviving more than 90 days post-transplant. Quite similar results have also been reported for hilar cholangiocarcinoma. Many of these patients underwent operations during the 1980s when the initial surgical endeavor was made to establish liver transplantation as a widespread treatment for liver diseases in general. Therefore, postoperative mortality rates are likely to be cut at least in half some 10 years later. However, the major obstacle to patient longevity remains again the unpredictable risk caused by potentially accelerated growth of residual tumor cells during chronic immunosuppression. This unfavorable experience is also reflected by a single center report of Pichlmayr et al. on 18 patients undergoing liver transplantation for cholangiocarcinoma [45]. None of the patients, including four patients suffering from T2 tumors survived beyond 2 years post-transplant. Disappointing long-term results after abdominal organ cluster transplantation were reported by Alessiani et al. [47, 48]. Among a variety of liver tumors, such as endocrine tumors, sarcoma, and hepatocellular carcinoma, cholangiocarcinoma fared the worst with a 5-year survival rate of 15%.

An unsolved problem which is still under debate is the usefulness of prophylactic liver transplantation for patients suffering from primary sclerosing cholangitis, a chronic inflammatory disease characterized by multiple fibrotic strictures throughout the biliary tree [49, 50]. In our own experience, the risk of occult peripheral cholangiocarcinoma or hilar duct cancer as a complication of PSC at the time of liver transplantation is 10%. This figure is within the scope of 9% to 15% reported in the literature [49, 51, 52, 53, 54]. The highest rate has been observed in Brisbane by Miros et al. [55]. In their liver transplantation program, 4 of 11 patients suffering from PSC had developed cholangiocarcinoma, i.e., a calculated risk of 36%. Some groups have concluded that the timing of liver transplantation for PSC should not only be related to the stage of the chronic inflammation and

its consecutive liver damage but that it should be brought forward to prevent the formation of biliary malignancies [56]. The rationale is a poor outcome after liver transplantation even in patients with low-grade malignancies. Others argue that PSC progresses slowly and can, over periods of more than 15 years or even longer, be managed by medical and endoscopic treatment [57] Therefore, many patients would unnecessarily undergo liver transplantation early in their life with a sometimes uncertain prognosis over the long term due to a diverse transplantation-associated morbidity. Thus, we follow the policy to transplant when indicated by the stage of PSC combined with efforts to keep the rate of occult cholangiocarcinoma in graft recipients low.

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